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Pulmonary function differences in patients with chronic right heart failure secondary to pulmonary arterial hypertension and chronic left heart failure

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Background: Pulmonary abnormalities are found in both chronic heart failure (CHF) and pulmonary arterial hypertension (PAH). The differences of pulmonary function in chronic left heart failure and chronic right heart failure are not fully understood.

Material/Methods: We evaluated 120 patients with stable CHF (60 with chronic left heart failure and 60 with chronic right heart failure). All patients had pulmonary function testing, including pulmonary function testing at rest and incremental cardiopulmonary exercise testing (CPX).

Results: Patients with right heart failure had a significantly lower end-tidal partial pressure of CO_2 ($PetCO_2$), higher end-tidal partial pressure of O_2 ($PetO_2$) and minute ventilation/CO_2 production (VE/VCO_2) at rest. Patients with right heart failure had a lower peak $PetCO_2$, and a higher peak dead space volume/tidal volume (VD/VT) ratio, peak $PetO_2$, peak VE/VCO_2, and VE/VCO_2 slope during exercise. Patients with right heart failure had more changes in $\Delta PetCO_2$ and $\Delta VE/VCO_2$, from rest to exercise.

Conclusions: Patients with right heart failure had worse pulmonary function at rest and exercise, which was due to severe ventilation/perfusion (V/Q) mismatching, severe ventilation inefficiency, and gas exchange abnormality.

MeSH Keywords: **Coronary Disease – rehabilitation • Heart Failure – prevention & control • Respiratory Function Tests – methods**

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Background

There are symptoms common to both chronic heart failure (CHF) and pulmonary arterial hypertension (PAH). The heart, lungs, kidneys, and muscles are affected in both diseases. Pulmonary abnormalities play an important role in the evaluation and prognosis of CHF and PAH. The differences of pulmonary function in chronic left heart failure and chronic right heart failure are not fully understood.

Cardiopulmonary exercise testing (CPX) is considered the criterion standard for studying cardiovascular, pulmonary, and metabolic adaptations to exercise in heart disease. Pulmonary abnormalities occur in both CHF and chronic right heart failure secondary to PAH [1–9]. Left heart failure with cardiac enlargement causes restrictive lung disease, interstitial edema, alveolar-capillary hydrostatic injury, and fatigue of respiratory muscles, which contributes to pulmonary abnormalities. PAH can cause ventilation/perfusion (V/Q) inequality secondary to pulmonary vascular bed damage. Hyperventilation may result from these pulmonary function changes.

We hypothesized that pulmonary function is different in patients with left heart failure and right heart failure secondary to PAH. This study may help understand relationships between pulmonary abnormalities and different types of heart failure.

Material and Methods

Patients

A single cardiologist evaluated 120 patients with clinically stable CHF, including 60 patients with chronic left heart failure and 60 patients with chronic right heart failure. Left heart failure was diagnosed using the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines for heart failure [10]. PAH was defined as WHO group1 PH according to the ACCF/AHA expert consensus document on pulmonary hypertension. We excluded patients with group 2, 3, 4, or 5, associated with congenital heart disease, portal hypertension, significant venous or capillary involvement, or persistent pulmonary hypertension of the newborn [11]. Right heart failure was defined as PAH and cardiac index (CI) <2.2 L/(min×m^2) as measured by right heart catheterization. All patients had symptoms and/or signs of right heart failure. All patients had a forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratio >65% at rest. All testing was performed before treatment.

The study protocol adhered to the Declaration of Helsinki. Each patient provided written informed consent to participate in this study. The document was approved and recorded by the institutional Ethics Committee of Fuwai Hospital, China. The project approval number was 2012-401.

Pulmonary function test at rest

Pulmonary function testing at rest was performed using a closed-circuit spirometer (COSMED, Italy) according to the American Thoracic Society (ATS) recommendations [12]. Dead space volume/tidal volume (VD/VT)=($PaCO_2$ – $PECO_2$ mean)/$PaCO_2$ – [VD (machine)/VT] where $PaCO_2$ = arterial CO_2 tension, $PECO_2$ = the partial pressure of expired CO_2. Minute ventilation/CO_2 production (VE/VCO_2) ratio was defined as VE/VCO_2 = 863/[$PaCO_2$ × (1-VD/VT)].

Cardiopulmonary exercise testing

Physician-supervised CPX was performed on a bicycle ergometer with a breath-by-breath system (COSMED, Italy) according to the ATS/American College of Chest Physicians (ACCP) Statement on CPX [13]. Exercise-induced right-to-left shunt (EIS) was performed according to criteria described by Sun [14].

Breathing reserve (BR) was defined as: BR = (MVV-peak VE)/MVV ×100% where MVV = maximal voluntary ventilation.

Change in CPX parameter from rest to peak exercise was defined as: Δ measure = (peak measure-rest measure)/rest measure ×100%.

Echocardiography

Two-dimensional echocardiography and Doppler ultrasound (Philips IE33, Netherlands) examinations were performed on the same day before CPX. Left ventricular ejection fraction (LVEF) was determined according to the recommendations of the European Association of Echocardiography [15].

Right heart catheterization

Right heart catheterization was performed 3 days after CPX. Pulmonary capillary wedge pressure (PCWP) and mean pulmonary artery pressure (mPAP) were determined with balloon flotation catheter (Edwards Lifesciences, USA). CI was determined by Frick method.

Statistical analyses

Data were analyzed using SPSS 13.0 (SPSS Inc; Chicago IL). Continuous variables are presented as mean ±SD and categorical variables as a percentage. The *t* test was used to compare continuous variables. The chi-square test was used to compare categorical variables. Multivariate linear regression was used to determine pulmonary function differences and the changes

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Table 1. Baseline characteristics.

Characteristic	Left heart failure (n=60)	Right heart failure (n=60)	P value
Men, n	53	10	<0.001
Age, years	45.1±9.9	30.8±9.5	<0.001
BMI, kg/m²	24.12±3.94	22.13±2.95	0.002
Smokers, n	37	4	<0.001
NYHA, n			0.131
Class I/II	18	27	–
Class III/IV	42	33	–
LVEF,%	27.92±8.99	64.65±6.31	<0.001
mPAP, mmHg	–	54.35±16.91	–
PCWP, mmHg	–	9.20±3.83	–
CI, L/min×m²	–	1.99±0.22	–
ICM, n	13	–	–
NICM, n	47	–	–
IPAH, n	–	44	–
FPAH, n		2	
APAH, n		14	

ICM – ischemic cardiomyopathy; NICM – non-ischemic cardiomyopathy; IPAH – idiopathic pulmonary arterial hypertension; FPAH – familial pulmonary arterial hypertension; APAH – associated with pulmonary arterial hypertension.

in CPX parameters between the 2 groups. To correct for demographic differences between the 2 groups of patients, variables that were either biologically plausible and/or significantly different between groups in univariate analysis were entered into the multivariate model. $P<0.05$ was considered statistically significant.

Results

Demographic data from the 2 patient groups are presented in Table 1. Patients with left heart failure were older, had a higher proportion of men and smokers, and had a higher BMI. These findings could affect pulmonary function.

The anaerobic threshold (AT) was detectable in all patients. Among the patients with right heart failure, 21 showed EIS. Table 2 shows the results of univariate analysis of pulmonary function. Patients with right heart failure had lower oxygen uptake (VO_2), VT, FEV1, FVC, MVV, and $PetCO_2$, and higher end-tidal partial pressure of O_2 ($PetO_2$) and VE/VCO_2 at rest. Right heart failure patients had lower peak VO_2, peak VE, peak VT, and peak $PetCO_2$, and had higher peak VD/VT, peak $PetO_2$, peak VE/VCO_2, and VE/VCO_2 slope during exercise. Right heart failure patients had lower ΔVO_2, ΔVE, $\Delta PetCO_2$, and $\Delta VE/VCO_2$, from rest to exercise.

Table 3 shows the result of multivariate regression analysis of pulmonary function. Patients with right heart failure had lower $PetCO_2$, and higher $PetO_2$ and VE/VCO_2 at rest. Right heart failure patients had a lower peak $PetCO_2$, and higher peak VD/VT, peak $PetO_2$, peak VE/VCO_2, and VE/VCO_2 slope during exercise. Right heart failure patients had lower $\Delta PetCO_2$ and $\Delta VE/VCO_2$, from rest to exercise.

Figure 1A shows the result of VD/VT ratio versus VE/VCO_2 at rest. The curves show patients with right heart failure had higher VE/VCO_2 and lower $PetCO_2$ at any given VD/VT ratio at rest. Figure 1B shows the result of peak $PetCO_2$ versus VE/VCO_2 slope. The abrupt curve of right heart failure was suggestive of EIS in the right heart failure patients during exercise. Most right heart failure patients had higher VE/VCO_2 slope and peak VD/VT at any given peak $PetCO_2$. Figure 1C shows the result of peak VD/VT ratio versus VE/VCO_2 slope. The curves show that most right heart failure patients had a lower $PetCO_2$ and higher VD/VT ratio at any given.

Discussion

Patients with right heart failure had lower $PetCO_2$, and higher $PetO_2$ and VE/VCO_2 at rest. Patients with right heart failure showed a higher peak VD/VT, peak $PetO_2$, peak VE/VCO_2, and VE/VCO_2 slope, and a lower $PetCO_2$ during exercise. Patients with right heart failure had more changes in $\Delta PetCO_2$ and $\Delta VE/VCO_2$ from rest to exercise. These results show that patients

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Table 2. Univariate analysis of pulmonary function.

Measure	Left heart failure	Right heart failure	P valure
Rest VO_2, ml/min	341.82±97.65	285.07±67.69	<0.001
Rest VE, L/min	11.09±3.16	10.42±2.75	0.214
Rest VT, L	0.68±0.20	0.59±0.22	0.028
Rest FEV1, L	2.89±0.57	2.55±0.59	0.001
Rest FVC, L	3.69±0.69	3.23±0.74	0.001
Rest FEV1/FVC, %	79.28±5.41	79.25±7.70	0.984
Rest MVV, L/min	118.27±28.62	97.17±27.12	<0.001
Rest Rf, b/min	17.02±4.69	18.82±5.44	0.054
Rest VD/VT, %	31.40±5.62	31.67±4.69	0.778
Rest $PetCO_2$, mmHg	33.72±4.47	28.78±4.25	<0.001
Rest $PetO_2$, mmHg	110.68±7.48	115.80±6.65	<0.001
Rest VE/VCO_2, L/min/L/min	37.96±6.50	43.45±6.79	<0.001
Peak VO_2, ml/min	1092.85±309.73	756.83±271.30	<0.001
Peak VE, L/min	43.62±11.79	36.91±14.71	0.007
Peak BR, %	61.80±9.77	63.83±12.19	0.315
Peak VT, L	1.47±0.41	1.19±0.36	<0.001
Peak Rf, b/min	30.30±6.01	31.24±8.04	0.468
Peak VD/VT, %	27.18±4.02	28.83±4.04	0.027
Peak $PetCO_2$, mmHg	33.42±6.04	24.32±5.30	<0.001
Peak $PetO_2$, mmHg	117.17±6.10	124.43±5.61	<0.001
Peak VE/VCO_2, L/min/L/min,	36.13±7.97	48.50±11.95	<0.001
VE/VCO_2 slope	32.74±7.52	45.70±16.18	0.001
EIS, n	–	21	
ΔVO_2, %	236.40±108.37	171.28±82.76	<0.001
ΔVE, %	323.56±168.47	262.41±118.19	0.023
ΔVT, %	126.49±59.07	114.34±68.37	0.300
ΔRf, %	88.70±58.52	72.89±45.66	0.054
ΔVD/VT, %	−11.71±15.45	−7.72±14.21	0.300
$\Delta PetCO_2$, %	−0.61±14.16	−15.61±12.91	<0.001
$\Delta PetO_2$,%	6.18±7.06	7.65±5.12	0.196
$\Delta VE/VCO_2$, %	4.55±16.28	−11.46±18.68	<0.001

Rf – respiratory frequency.

with right heart failure had worse pulmonary function at rest and exercise.

Pulmonary function at rest

Pulmonary function changes compatible with restrictive lung disease are observed in most patients with severe CHF [16,17], and findings compatible with airway obstruction are common in patients with right heart failure caused by idiopathic pulmonary arterial hypertension (IPAH) [18]. We did not observed any different ventilatory measures at rest in the 2 groups.

$PetCO_2$ reflects ventricular function [19]. Right heart failure patients had a lower $PetCO_2$ (Table 3, Figure 1A). Figure 1A

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Table 3. Multivariate regression analysis of pulmonary function.

Measure	β	P value
Rest VO_2, ml/min	−0.052	0.700
Rest VT, L	0.058	0.687
Rest FEV1, L	−0.139	0.304
Rest FVC, L	−0.004	0.977
Rest MVV, L/min	−0.049	0.705
Rest Rf, b/min	0.064	0.664
Rest $PetCO_2$, mmHg	−0.435	0.001
Rest $PetO_2$, mmHg	0.329	0.023
Rest VE/VCO_2, L/min/L/min	0.320	0.020
Peak VO_2, ml/min	−0.174	0.118
Peak VE, L/min	0.213	0.102
Peak VT, L	0.179	0.149
Peak VD/VT,%	0.376	0.010
Peak $PetCO_2$, mmHg	−0.704	<0.001
Peak $PetO_2$, mmHg	0.655	<0.001
Peak VE/VCO_2, L/min/L/min,	0.614	<0.001
VE/VCO_2 slope	0.506	0.001
ΔVO^2, %	−0.195	0.171
ΔVE, %	0.003	0.984
ΔRf, %	−0.081	0.591
$\Delta PetCO_2$,%	−0.657	<0.001
$\Delta VE/VCO_2$, %	−0.622	<0.001

Left heart failure = 0, right heart failure = 1, female = 0, male = 1, non-smoker = 0, smoker = 1.

shows that right heart failure patients had a lower $PetCO_2$ at any given VD/VT. These results demonstrate that patients with right heart failure had more ventilation at given CO_2 discharge. Considering there was no difference in respiratory frequency or VE, the lower $PetCO_2$ was due to hyperventilation in alveolus with well-perfusion and hypoperfusion of well ventilated alveolus in patients with right heart failure [20,21]. The lower $PetCO_2$ could explain the higher VE/VCO_2 in patients with right heart failure. The higher VE/VCO_2 showed that right heart failure patients had lower ventilation efficiency. The higher $PetO_2$ was a secondary effect of lower $PetCO_2$.

The VD/VT ratio reflects the V/Q mismatching [20]. There was no difference in VD/VT ratio between the 2 groups. This result means that there was no difference in V/Q mismatching at rest in the 2 groups.

Pulmonary function during exercise

$PetCO_2$ was lower in both CHF and PAH, reflecting the ventilation impairment [3,8,20–25]. We found that right heart failure patients had a lower $PetCO_2$ during exercise (Table 3). The reason for the lower peak $PetCO_2$ during exercise in patients with right heart failure was similar to the reason for lower $PetCO_2$ at rest. Sun et al. [14] found that patients with PAH had an EIS resulting in abrupt decreased $PetCO_2$, had increased $PetO_2$, and increased VE/VCO_2 ratio during exercise. The abrupt curve of right heart failure demonstrated that patients with right heart failure had EIS (Figure 1B). EIS also contributed to the lower peak $PetCO_2$.

We found that patients with right heart failure had significantly higher peak VD/VT ratio (Table 3). Figure 1C shows that most patients with right heart failure had a lower peak $PetCO_2$ and a higher VE/VCO_2 slope. These results demonstrate that patients with right heart failure had severe V/Q mismatching at peak exercise. This means that primary pulmonary vesicular damage played a greater role in V/Q mismatching during exercise than did pulmonary congestion. Moreover, the EIS was involved in the higher VD/VT in patients with right heart failure.

VE/VCO_2 and VE/VCO_2 slope are important to reflect disease severity and prognosis in CHF and PAH, and reflect V/Q mismatching in PAH [21,25]. We found that peak VE/VCO_2 and VE/VCO_2 slope were higher in patients with right heart failure. These results demonstrate that patients with right heart failure had more severe ventilation inefficiency and gas exchange abnormality compared to patients with left heart failure. These results were due to lower peak $PetCO_2$ and higher peak VD/VT in right heart failure patients.

Change in CPX parameters from rest to peak exercise

We found that patients with right heart failure had higher absolute values of $\Delta PetCO_2$ and $\Delta VE/VCO_2$ from rest to peak exercise (Table 2 and 3). These results show that right heart failure patients had larger changes of pulmonary function from rest to exercise. The larger change of $\Delta PetCO_2$ demonstrates that patients with right heart failure had more severe hyperventilation from rest to exercise. This should be attributed to more complex ventilation drive in PAH, including exercise-induced hypoxia and EIS [20].

We found that patients with right heart failure had worse ventilation efficiency, severe V/Q mismatching, and gas exchange abnormality, even without differences in peak VO_2.

This study had some limitations. It was a single-center study and demographic differences were detected between the 2 groups. The etiology of heart failure in the 2 groups resulted in differences of sex and age. Because there was no control group, we could not confirm a normal breathing pattern

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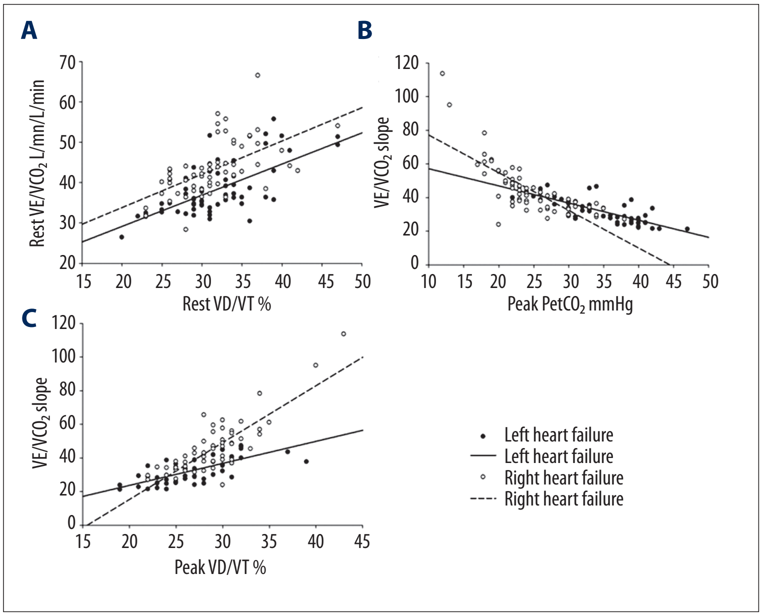

Figure 1. (A) VD/VT ratio versus VE/VCO_2 at rest. The curves showed that patients with right heart failure had a higher VE/VCO_2 at any given VD/VT ratio at rest. (**B**) Peak $PetCO_2$ versus VE/VCO_2 slope. The abrupt curve of right heart failure was suggestive of EIS in the right heart failure patients during exercise. (C) Peak VD/VT ratio versus VE/VCO_2 slope. The curves showed that most right heart failure patients had a lower $PetCO_2$ at any given VD/VT ratio.

at rest. We could not obtain diffusion function measures from all patients. This influenced the evaluation of pulmonary function. We could not perform invasive hemodynamic testing in all patients, which influenced our evaluation of left heart failure. We merged the 4 disease classes into 2 groups because there were not enough patients with class IV NYHA right heart failure.

Conclusions

Patients with right heart failure had worse pulmonary function at rest and during exercise. The differences in pulmonary function at rest were due to different breathing patterns and worse gas exchange in patients with right heart failure. The differences during exercise were due to severe V/Q mismatching, EIS, alveolar ventilation disorder, and oxygenation dysfunction secondary to pulmonary vascular damage in patients with right heart failure.

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